World Health Organization

European Region

Review of antibiotics in national medicines selection lists

in eastern Europe and central Asia

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Abstract

This report presents results of a review of antibiotics contained in national medicines selection lists of 18 non-European Union Member States in the WHO European Region. The review compared antibiotics in national medicines selection lists used in WHO European Region countries in eastern Europe and central Asia, with the 2019 WHO Model List of Essential Medicines for adults, and with the WHO Access, Watch and Reserve classification. The review also examined how antibiotic inclusion in lists correlated with measured consumption rates. Through the activities of the WHO Europe Antimicrobial Medicines Consumption Network, the WHO Regional Office for Europe and its partners remain committed to supporting Member States to improve their use of antibiotics.

Keywords

ANTIBIOTICS
ESSENTIAL MEDICINES
ANTIMICROBIAL MEDICINES CONSUMPTION (AMC)
ANTI-INFECTIVE AGENTS – THERAPEUTIC USE
RESPONSIBLE USE OF ANTIBACTERIALS
EASTERN EUROPE AND CENTRAL ASIA

ISBN: 978-92-890-5858-2

Designed by: Phoenix Design Aid, Denmark

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ABBREVIATIONS

AMC	antimicrobial medicines consumption
AMR	antimicrobial resistance
API	active pharmaceutical ingredient
AWaRe	WHO Access, Watch and Reserve (classification)
CPL	centralised procurement list
DDD	defined daily dose
EML	WHO Model List of Essential Medicines for adults
EPW	European Programme of Work, 2020–2025
FDC	fixed-dose combination
MDR-TB	multidrug-resistant tuberculosis
NEML	national essential medicines list
RL	reimbursement list
UHC	universal health coverage

Abbreviations of country names used in some tables and figures

ALB	Albania
ARM	Armenia
AZE	Azerbaijan
BLR	Belarus
BIH	Bosnia and Herzegovina
GEO	Georgia
KAZ	Kazakhstan
KGZ	Kyrgyzstan
MDA	Republic of Moldova
MNE	Montenegro
MKD	North Macedonia
RUS	Russian Federation
SRB	Serbia
TJK	Tajikistan
TUR	Türkiye
UKR	Ukraine
UZB	Uzbekistan

ACKNOWLEDGEMENTS

The WHO Regional Office for Europe would like to thank the WHO Europe Antimicrobial Medicines Consumption (AMC) Network members for providing antimicrobial consumption data and for their valuable contributions to this report.

The report was written by Albert Figueras, Dzintars Gotham, and Kotoji Iwamoto (Access to Medicines and Health Products, WHO Regional Office for Europe); and it was reviewed by Jane Robertson (Access to Medicines and Health Products, WHO Regional Office for Europe), Lorenzo Moja, Benedikt Huttner, and Bernadette Cappello (Essential Medicines, WHO Headquarters).

WHO Europe AMC Network activities are coordinated by the WHO Regional Office for Europe. The financial support of the Ministry of Health, Welfare and Sport of the Netherlands and of the German Collaboration Programme is gratefully acknowledged.

BACKGROUND

As presented in the European Programme of Work, 2020–2025 –"United Action for Better Health" (EPW), Member States of WHO globally, including WHO's European Region, are committed to implementing three interconnected strategic priorities:

- Core Priority 1). Moving towards universal health coverage (UHC);
- Core Priority 2). Protecting against health emergencies;
- Core Priority 3). Promoting health and well-being. Reducing inappropriate prescribing, promoting rational prescribing, and surveying antimicrobial use are the activities emphasized under Core priority 3 *(1)*. The EPW is aligned with the Global Action Plan on antimicrobial resistance (AMR), which calls for "optimizing the use of antimicrobial agents" as one of its five objectives *(2)*.

The WHO Model List of Essential Medicines (EML) serves as a guide for developing and updating national and institutional medicines selection lists, to satisfy the priority health-care needs of the population *(3)*. In the 2017 update of the EML, WHO proposed a new classification of antibiotics, the Access, Watch and Reserve (AWaRe) classification, in the context of a comprehensive review of the optimal antibiotic choices for many common infectious syndromes in adults and children *(4)*. In 2019 and 2021, the AWaRe classification was reviewed and expanded to include the most widely available antibiotics and to reflect experiences with using the classification since it was first published in 2017 *(5)*. WHO recommends using the AWaRe classification to monitor antibiotic consumption, optimize antibiotic use, and serve as a tool for antibiotic stewardship at the national level. Countries can adopt policies to use the AWaRe classification to optimize antibiotic use and strengthen stewardship actions through supporting prescribers, pharmacists, antibiotic stewards, and policy-makers to address the AMR challenge. Along with creating the new EML (2021), WHO has published the WHO AWaRe antibiotic book, which intends to provide guidance on empiric antibiotic treatment for countries without domestic antibiotic prescribing guidelines *(6)*.

WHO suggests that national essential medicines lists (NEMLs) be aligned with the EML *(7)*. However, a 2021 WHO global review of NEMLs for 138 countries found that 72 countries' NEMLs (52%) prioritized Watch and Reserve group antibiotics over Access group antibiotics *(8)*. In fact, antimicrobial consumption data from the WHO Europe Antimicrobial Medicines Consumption (AMC) Network indicate low utilisation in national markets of some essential Access group antibiotics, such as, phenoxymethylpenicillin and flucloxacillin *(9)*. These antibiotics may be included in a country's NEML but rarely prescribed in practice, or they may not be included in a country's NEML (or in similar lists influencing procurement). In either case, unavailability of essential antibiotics in the national market may hinder antimicrobial stewardship efforts.

Antibiotics on the EML should be prioritized for procurement and distribution. Deviations from the EML should be justified (for example, by documented differences in the epidemiology of pathogens causing infections and their resistance profiles) *(7)*. Indeed, many countries use medicines selection lists to guide pharmaceutical financing, procurement and use. Different health systems employ different types of medicines selection lists, depending on the structure and needs of a given health system. There are three types of medicines selection lists commonly seen: NEML, reimbursement list (RL, also known as "positive list"), and central procurement list (CPL). These lists were identified for countries in eastern Europe and central Asia, in the WHO European Region. However, there is limited knowledge regarding the extent to which such lists actually guide procurement and clinical practice in the countries included in this review, and more understanding of the local contexts will be needed to utilize the findings of this review.

The EML AWaRe classification. To assist in the development of tools for antibiotic stewardship at local, national and global levels and to reduce AMR, the AWaRe tool was developed to classify antibiotics into different groups, thereby emphasizing the importance of their appropriate use.

Access Group Antibiotics
This group includes antibiotics that have activity against a wide range of commonly encountered pathogens, while also evidencing lower resistance potential than antibiotics in the other groups. Selected Access group antibiotics are recommended as essential first- or second-choice empiric treatment options for infectious syndromes reviewed by the EML Expert Committee and are listed as individual medicines on the Model Lists to improve access and promote appropriate use. These are essential antibiotics that should be widely available, affordable and quality-assured.

Watch Group Antibiotics
This group includes antibiotics that have higher resistance potential. This group includes most of the highest priority agents among the Critically Important Antimicrobials for Human Medicine and/or antibiotics that are at relatively high risk to acquire bacterial resistance. These medicines should be key targets of stewardship programmes and monitoring. Selected Watch group antibiotics are recommended as essential first- or second-choice empiric treatment options for a limited number of specific infectious syndromes. They are listed as individual medicines on the Model Lists.

Reserve Group Antibiotics
This group includes antibiotics that should be reserved for treatment of confirmed or suspected infections due to multidrug-resistant organisms. Reserve group antibiotics should be treated as "last-resort" options. Selected Reserve group antibiotics are listed as individual medicines on the Model Lists when they have a favourable risk-benefit profile and proven activity against "Critical Priority" or "High Priority" pathogens identified by the WHO Priority Pathogens List, notably carbapenem-resistant Enterobacteriaceae. These antibiotics should be accessible, but their use should be tailored to highly specific patients and settings, when all alternatives have failed or are not suitable. These medicines should be key targets of national and international stewardship programmes involving monitoring and reporting, thereby preserving their effectiveness.

Source: *(5)*.

AIM OF THE REVIEW

This review aimed to compare antibiotics in national medicines selection lists that are used in WHO European Region countries in eastern Europe and central Asia, with the 2019 EML and with AWaRe classification. The review also aimed to examine the correlation of antibiotic inclusion in country lists, with measured consumption rates. The following questions were examined:

1. To what extent are the EML-recommended antibiotics included in national medicines selection lists?
2. Do AWaRe classifications have any correlation with the inclusion rate of the EML-recommended antibiotics in the national medicines selection lists?
3. Do national medicines selection lists incorporate the AWaRe classification system?
4. Are there countries where the first-choice antibiotics recommended in the AWaRe Antibiotic Book are missing from national medicines selection lists?
5. Do national medicines selection lists include antibiotics that are not in the EML?
6. Is there a correlation between how many EML-recommended antibiotics are included in national medicines selection lists, and antibiotic consumption?

This analysis covered 17 countries in eastern Europe and central Asia in the WHO European Region.

METHODOLOGY

National medicines selection lists

There were actually three types of national medicines selection lists identified for this review: NEML, RL and CPL. Differences between these types of lists are not discussed here, but are outlined elsewhere *(10, 11)*.

NEMLs, RLs, and CPLs were collected from public websites, as well as through WHO Country Offices and focal points of the WHO Europe AMC Network from May to July 2021. Where multiple medicines selection lists were available for one country, all lists dated within the last three years, 2018–2021, were included. If no lists for that time period were available, the most recent available list was used. A dataset of antibiotics and formulations included in each NEML, RL, and CPL was compiled. Where more than one type of list was identified for a country, the lists were combined cumulatively. Lists were analysed in terms of correlation with the 2019 EML and with the AWaRe classification system *(12)*. In the 2019 AWaRe classification, 180 essential antibiotics are divided into Access (n = 48), Watch (n = 110), or Reserve (n = 22) groups. The 2019 EML lists 19 Access, 11 Watch, and seven Reserve group antibiotics *(5)*. The 2021 edition of EML was published in November 2021, after the collection of national selection lists for this analysis had been completed. Therefore, the 2019 edition of EML was used in this analysis, as it was considered unlikely that by the time of data collection, countries would have already updated their lists to reflect proposed changes in 2021.

EML does not include topical and inhalational formulations for antibiotics (creams, ointments, suppositories, inhalational formulations)[1], and this analysis excluded all of those formulations. Medicines whose clinical use is normally limited to tuberculosis and leprosy and/or which are listed in the applicable sections of EML were also excluded from the analysis[2].

"Square box" medicines

For some antibiotics, the 2019 EML suggests acceptable alternatives ("square box listing") *(5)*:

- for cloxacillin: dicloxacillin and flucloxacillin are listed as alternatives with no limitations;
- for clarithromycin: erythromycin is listed as an alternative with no limitations;
- for sulfamethoxazole + trimethoprim: trimethoprim is listed as an alternative for use in one indication (lower urinary tract infection);
- for meropenem: imipenem/cilastatin is listed as an alternative except for acute bacterial meningitis, where meropenem is preferred.

1 With the exception of metronidazole in suppository form.
2 For example, rifampicin, rifabutin, amikacin, levofloxacin, moxifloxacin, streptomycin.

AMC data

AMC data from the third WHO Europe AMC Network report (2018) were used. Consumption of antibiotics is expressed in defined daily doses (DDD) per 1,000 inhabitants per day *(13)*.

In some contexts, DDD values were converted into the estimated number of people, per country, who received a certain antibiotic on any given day in 2018. The 2019 AWaRe system was used to classify the antibiotics.

The relative consumption levels for antibiotics in the AWaRe groups were calculated to analyse antibiotic inclusion in national medicines selection lists with regard to AWaRe groups. The WHO 13th General Programme of Work 2019–2023 has adopted a corresponding indicator: Access group antibiotics at ≥ 60% of overall antibiotic consumption *(14)*.

FINDINGS

To what extent are EML-recommended antibiotics included in national medicines selection lists?

National medicines selection lists identified in this analysis are outlined in Table 1. For 15 of the 17 countries included in this analysis, it was possible to identify, obtain, and analyse one or more medicines selection lists dated in the last three years. For Georgia, the most recent available list was a NEML from 2007; for Azerbaijan, the most recent available list was a NEML from 2016. Across countries, the most common type of list identified was a NEML (15 of 17 countries), with the next most common type of list being an RL (11 of 17 countries), and the least common type of list being a CPL (7 of 17 countries).

Table 1. National medicines selection lists identified for this analysis

Country	NEML			RL			CPL		
	Identified	Year	Used in analysis	Identified	Year	Used in analysis	Identified	Year	Used in analysis
ALB	✓	2011	No	✓	2019	Yes	✓	2021	Yes
ARM	✓	2018	Yes	✗	–	No	✗	–	No
AZE	✓	2016	Yes	✗	–	No	✗	–	No
BIH	✓	2009	No	✓	2019	Yes	✗	–	No
BLR	✓	2020	Yes	✗	–	No	✓	2020	Yes
GEO	✓	2007	Yes	✗	–	No	✗	–	No
KAZ	✓	2021	Yes	✓	2021	Yes	✓	2020	Yes
KGZ	✓	2018	Yes	✓	2018	Yes	✗	–	No
MDA	✓	2011	No	✓	2021	Yes	✓	2021	Yes
MKD	✓	2015	No	✓	2021	Yes	✗	–	No
MNE	✓	2011	No	✓	2020	Yes	✓	2020	Yes
RUS	✓	2019	Yes	✓	2021	No[a]	✗	–	No
SRB	✗	–	No	✓	2021	Yes	✗	–	No
TJK	✓	2020	Yes	✗	–	No	✓	2021	Yes
TUR	✗	–	No	✓	2018	Yes	✗	–	No
UKR	✓	2017	Yes	✓	2021	No[b]	✓	2018	No[c]
UZB	✓	2018	Yes	✗	–	No	✗	–	No

[a] List sets price limits for medicines on the NEMLs.
[b] List covers noncommunicable diseases only.
[c] List includes numerous antibiotics, but only in the context of treating children with oncological disease. As this is a small proportion of all patients needing antibiotics, this list was excluded from analysis.

An overview of the EML-recommended antibiotics included in national medicines selection lists is given in Table 2. As stated earlier in this report, the 2019 EML shows 19 Access, 11 Watch and seven Reserve group antibiotics. Oral and parenteral formulation of metronidazole (Access) and vancomycin (Watch) are included individually; thus, a denominator of 39 was used as the total number of antibiotics. Overall, the country with the highest proportion of the EML-recommended antibiotics included in its national medicines selection list(s) was Armenia, with 33 of 39 (85%) EML antibiotics. The country with the lowest proportion of EML antibiotics that were included in its national medicines selection list(s) was North Macedonia (26%). Most countries included over 50% of EML-recommended antibiotics in their national medicines selection lists.

Table 2. In national medicines selection lists, inclusion of the antibiotics recommended by the 2019 EML

Agent	ALB	ARM	AZE	BIH	BLR	GEO	KAZ	KGZ	MDA	MKD	MNE	RUS	SRB	TJK	TUR	UKR	UZB	Total
Access																		
Amikacin	✓	✓	✓	✓	✓	–	✓	✓	✓	–	✓	✓	✓	✓	✓	✓	✓	15
Amoxicillin	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	17
Amoxicillin/ clavulanic acid	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	17
Ampicillin	✓	✓	✓	✓	✓	✓	✓	✓	✓	–	✓	✓	✓	✓	✓	✓	✓	16
Benzathine benzylpenicillin	✓	✓	✓	–	(✓[d])	✓	✓	✓	(✓[d])	–	✓	✓	–	✓	✓	✓	✓	12
Benzylpenicillin	✓	✓	–	✓	✓	✓	✓	✓	✓	–	–	✓	✓	✓	✓	✓	✓	14
Cefalexin	✓	✓	–	✓	✓	–	–	✓	✓	✓	✓	✓	✓	✓	✓	✓	–	13
Cefazolin	✓	✓	✓	✓	✓	–	✓	✓	✓	–	✓	✓	✓	✓	✓	✓	✓	15
Chloramphenicol	✓	✓	✓	✓	✓	✓	✓	✓	✓	–	✓	✓	–	✓	–	✓	✓	14
Clindamycin	–	✓	–	✓	–	✓	–	✓	–	–	✓	✓	✓	✓	✓	✓	–	10
Cloxacillin, dicloxacillin, or flucloxacillin	–	✓	–	✓	–	–	–	–	–	–	✓	–	–	✓	–	✓	–	6
Doxycycline	✓	✓	–	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	16
Gentamicin	✓	✓	✓	✓	✓	✓	✓	✓	✓	–	✓	✓	✓	✓	✓	✓	✓	16
Metronidazole (IV)	✓	✓	✓	✓	–	✓	✓	✓	✓	–	✓	✓	✓	✓	✓	✓	✓	15
Metronidazole (oral)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	–	✓	–	✓	✓	✓	✓	15
Nitrofurantoin	✓	✓	✓	–	✓	✓	✓	✓	–	–	–	–	–	✓	✓	✓	–	10
Phenoxymethylpenicillin	–	✓	–	✓	–	✓	–	✓	–	(✓[c])	✓	✓	–	✓	✓	✓	–	9
Procaine benzylpenicillin	–	✓	–	✓	–	✓	(✓[d])	–	–	–	(✓[d])	–	(✓[d])	✓	–	✓	–	5
Spectinomycin	–	✓	–	–	–	✓	–	✓	–	–	–	–	–	✓	–	✓	–	5
Sulfamethoxazole/ trimethoprim[a]	✓	✓	✓	✓	✓	✓	✓	✓	✓	–	✓	✓	✓	✓	✓	✓	✓	16
Watch																		
Azithromycin	✓	✓	–	✓	✓	–	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	15
Cefixime	✓	✓	–	✓	–	–	✓	✓	✓	✓	✓	–	✓	✓	✓	✓	–	12
Cefotaxime	–	✓	–	✓	✓	–	✓	✓	✓	–	–	✓	✓	✓	✓	✓	✓	12
Ceftazidime	✓	✓	–	✓	–	–	✓	✓	✓	–	✓	✓	✓	✓	✓	✓	✓	13
Ceftriaxone	✓	✓	✓	✓	–	✓	✓	✓	✓	–	✓	✓	✓	✓	✓	✓	✓	15
Cefuroxime	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	–	✓	–	✓	15
Ciprofloxacin	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	17
Clarithromycin or erythromycin	✓	✓	–	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	16

Table 2 contd.

Agent	ALB	ARM	AZE	BIH	BLR	GEO	KAZ	KGZ	MDA	MKD	MNE	RUS	SRB	TJK	TUR	UKR	UZB	Total
Meropenem[b]	✓	✓	(✓[b])	(✓[b])	(✓[b])	–	✓	✓	✓	–	✓	✓	✓	(✓[b])	✓	✓	✓	11 (15[b])
Piperacillin/ tazobactam	✓	✓	–	–	✓	–	✓	–	✓	–	✓	–	✓	–	✓	✓	✓	10
Vancomycin (IV)	✓	✓	–	✓	–	✓	–	✓	✓	–	✓	✓	✓	✓	✓	✓	–	12
Vancomycin (oral)	–	✓	–	–	–	–	–	–	–	–	–	✓	–	–	–	–	✓	3
Reserve																		
Ceftazidime/ avibactam	–	–	–	–	–	–	–	–	–	–	–	✓	–	–	–	–	–	1
Colistin	✓	–	–	–	✓	–	✓	–	✓	–	✓	–	✓	–	✓	–	–	7
Fosfomycin (IV)	–	–	–	✓	–	–	–	–	–	–	–	✓	–	–	–	✓	–	3
Linezolid	–	✓	–	–	✓	–	✓	✓	✓	–	–	✓	✓	✓	✓	✓	✓	11
Meropenem/ vaborbactam	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0
Plazomicin	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0
Polymyxin B	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0
% of EML antibiotics in national list	**69%**	**85%**	**38%**	**69%**	**54%**	**54%**	**69%**	**74%**	**67%**	**26%**	**67%**	**74%**	**64%**	**74%**	**74%**	**82%**	**62%**	

[a] Trimethoprim (as monotherapy) is listed as an alternative to sulfamethoxazole/trimethoprim combination, for some indications, in WHO EML. Trimethoprim was included in lists in Armenia and Tajikistan. There were no countries/territories where trimethoprim was listed whilst sulfamethoxazole/trimethoprim was not.

[b] Imipenem/cilastatin is listed as an alternative to meropenem, for some indications, in EML. Values in parentheses represent listing of Imipenem/ cilastatin when meropenem was not listed. Imipenem/cilastatin was included in lists in ALB, ARM, AZE, BIH, BLR, KAZ, KGZ, MDA, MNE, RUS, SRB, TJK, TUR, UKR, UZB. In AZE, BIH, BLR, and TJK, Imipenem/cilastatin was listed but meropenem was not.

[c] Available only as benzathine phenoxymethylpenicillin.

[d] Not available as monotherapy but available as part of a combination.

Amoxicillin, amoxicillin with clavulanic acid (Access) and ciprofloxacin (Watch) were included in all 17 countries' lists. Certain EML-recommended antibiotics stood out by being included in national medicines selection lists less often than others (Table 2). In the Access group, cloxacillin (and its alternatives dicloxacillin and flucloxacillin), procaine benzylpenicillin and spectinomycin were notably less common in national medicines selection lists, included in six, five and five lists, respectively. In the Watch group, oral vancomycin was notably less often included in lists compared to other EML-recommended antibiotics in this AWaRe group. In the Reserve group, most EML-recommended antibiotics were not listed in most countries; by contrast, linezolid stood out as the most included antibiotic, being in 11 lists.

Discussion and limitations of international comparisons

Linezolid was present in national medicines selection lists far more often than other Reserve group antibiotics. This may be related to its use for multidrug-resistant tuberculosis (MDR-TB), as linezolid is also listed for this indication in the EML, in addition to its use against vancomycin-resistant and methicillin-resistant *Staphylococcus aureus*. The low rate of inclusion of the other Reserve antibiotics across countries is consistent with the very low consumption levels for Reserve group antibiotics reported in the countries included in this study *(13)*. Essential Reserve antibiotics should be available in country health systems for cases where other antibiotics have failed. The key challenge is to ensure their appropriate use; it is therefore critical that policies for the usage of Reserve antibiotics, infrastructure for policy implementation, and a monitoring system are in place prior to introduction of Reserve group antibiotics.

Only medicines selection lists identified and chosen according to certain criteria were included in the analysis. Additionally, countries vary significantly in the types of medicines selection lists they use. Therefore, international comparisons must be treated with caution. Apparent low concordance of national medicines selection lists with the EML may reflect the specific local role of such lists, rather than true unavailability of antibiotics in the national market. For example, the lists analysed for BIH, MKD, SRB, TUR are relevant only to the outpatient setting. Thus, the medicines available at the hospital level in these countries can be different. This may also explain the results related to Reserve antibiotics, which are used mostly in hospitals to treat drug-resistant infections. Similarly, the extent to which CPLs are implemented in procurement decisions may vary country to country. For example, in BLR, the CPL is used only for purchasing foreign medicines, a process that requires tendering. However, locally manufactured medicines can be sold directly to the health facilities without tendering. This needs to be taken into consideration when findings are being interpreted.

Do AWaRe classes correlate with the inclusion rate of EML-recommended antibiotics in the national medicines selection lists?

Inclusion levels varied notably between AWaRe groups (Table 3). For Access group antibiotics, the median inclusion rate was 80% (range 25–100%). Similarly, for Watch group antibiotics, the median rate was 83% (range 25–100%). Inclusion levels were lower for Reserve group antibiotics, with a median inclusion rate of 14% (range 0–29%).

Table 3. Proportion of EML-recommended antibiotics included in national lists

Country	Access	Watch	Reserve	Overall
ARM	100%	100%	14%	**85%**
UKR	100%	83%	29%	**82%**
RUS	80%	83%	43%	**74%**
TJK	100%	67%	14%	**74%**
TUR	80%	92%	29%	**74%**
KGZ	85%	83%	14%	**72%**
ALB	80%	83%	14%	**69%**
BIH	85%	75%	14%	**69%**
KAZ	70%	92%	29%	**69%**
MDA	65%	92%	29%	**67%**
MNE	75%	83%	14%	**67%**
SRB	60%	92%	29%	**64%**
UZB	65%	83%	14%	**62%**
GEO	80%	42%	0%	**54%**
BLR	65%	50%	29%	**54%**
AZE	60%	25%	0%	**38%**
MKD	25%	42%	0%	**26%**

Do national medicines selection lists incorporate the AWaRe classification system?

The NEML in Ukraine (published December 2017) has a "primary antibiotics" section and a section for "other antibiotics". These two sections have relatively good concordance with the AWaRe system, but they do not directly reference it. It should be noted that the AWaRe system, as part of the 2017 (20th) EML, was first published only a few months earlier than the publication of Ukraine's NEML.

None of the other medicines selection lists reviewed in this analysis used the AWaRe system or a different prioritization (such as, first-line versus second-line) system for antibiotics.

Discussion

The AWaRe classification recommended by WHO as a tool for antibiotic stewardship is a relatively new tool. It was first developed by WHO in 2017 and underwent revisions by the EML Expert Committees convened in 2019 and 2021. These frequent changes may have been a challenge for the tool's implementation at the national level. A systematic review conducted in 2022 to estimate associations between exposure to antibiotics and isolation of multidrug-resistant bacteria demonstrated stronger associations for Watch and Reserve antibiotics than for Access antibiotics. It suggested that optimizing the use of Access antibiotics could reduce the selection of multidrug-resistant bacteria and AMR. The finding has reinforced the rationale for the adoption of the AWaRe classification as a tool for improving antibiotic prescribing *(15)*.

Are there countries where the first-choice antibiotics recommended in the WHO AWaRe antibiotic book are missing from national medicines selection lists?

The WHO AWaRe antibiotic book is a resource to help countries and health-care systems implement responsible use of antibiotics recommended by WHO for specific infections and contained in the EML. The book recommends which antibiotics to use for common infectious diseases in both primary care and hospitals *(6)*. Thus, listing of the first-choice antibiotics in the national medicines selection lists was assessed.

A total of five countries did not list benzathine benzylpenicillin, which is the only recommended option for managing syphilis, according to the WHO AWaRe antibiotic book *(6)*. There were seven countries that did not have phenoxymethylpenicillin (penicillin V) listed, and eight countries did not have nitrofurantoin listed. Amoxicillin is recommended by the WHO AWaRe antibiotic book as an alternative for phenoxymethylpenicillin when used for common infections such as pharyngitis, and amoxicillin + clavulanic acid is recommended as an alternative to nitrofurantoin for lower urinary tract infection. In all countries where phenoxymethylpenicillin or nitrofurantoin were not listed, amoxicillin and amoxicillin + clavulanic acid, respectively, were listed. All the remaining first-choice antibiotics recommended in the AWaRe antibiotic book were on national medicines selection lists.

Discussion

The relevance of EML-recommended antibiotics being absent from national lists depends on the specific antibiotic and its recommended use, as well as the availability of other recommended alternatives. For example, the antibiotics recommended in the WHO AWaRe antibiotic book to manage the most frequent infectious conditions in primary health care are often Access group

antibiotics for which resistance levels are low. In cases where the national list does not include more first-choice options, prescribers may jump to second-choice antibiotics, which are usually in the Watch group. This is the case for phenoxymethylpenicillin (penicillin V) and nitrofurantoin, and their unavailability could require the prescription of antibiotics such as macrolides or fluoroquinolones, considered second-choice options because they are Watch group antibiotics. As suggested by a recent meta-analysis, switching to Watch group antibiotics is associated with an increase in bacterial resistance *(15)*.

Penicillins with a narrow spectrum of activity continue to be useful in areas with lower resistance rates. However, the panorama can be complicated by possible shortages of some antibiotics. Research conducted by WHO on active pharmaceutical ingredient (API) producers of antibiotics found that there were only two API producers supplying the API for over half of approved products for 10 antibiotics: amoxicillin-clavulanic acid, benzathine penicillin, piperacillin-tazobactam, cefepime, imipenem + cilastatin, meropenem, gentamicin, sulfamethoxazole + trimethoprim, and fosfomycin *(16)*.

Do national medicines selection lists include antibiotics that are not in the EML?

Most medicines selection lists included numerous antibiotics that are not listed as essential in the EML (non-EML antibiotics) (Tables 4A and 4B). TUR (n = 25 non-EML antibiotics), RUS (17) and KAZ (16) were the countries with the largest number of non-EML antibiotics included in their lists. In these countries, the proportion of non-EML antibiotics on national lists represented 46.3%, 36.9%, and 37.2%, respectively. However, national medicines selection lists play different roles in different countries. The inclusion of a wide variety of antibiotics, including many antibiotics not on the EML, does not necessarily imply regular use of non-EML antibiotics; for example, local guidelines may prioritize agents, and non-EML antibiotics may be reserved for use in selected cases under microbiologist guidance.

These non-EML antibiotics can be classified into categories:

1. antibiotics that have been removed from the EML but are still included in national medicines selection lists; and

2. antibiotics that have never been recommended in the EML.

Based on AMC data of 2018, estimates were calculated for the average number of persons that received non-EML antibiotics on any given day, in each studied country. Across all the studied countries, consumption data showed that, on any given day, an average of six million people of a total population of 383.7 million (1.6%) were being treated with EML-recommended antibiotics, and 1.3 million (0.4%) were being treated with non-EML antibiotics.

1. Antibiotics that have been removed from the EML but are still included in national medicines selection lists

Tables 4A and 4B include some antibiotics that have been removed from the EML but are still present in some national medicines selection lists. These include certain Watch group antibiotics (such as, cefepime, ofloxacin, kanamycin) and Reserve group antibiotics (such as, ceftaroline fosamil, tigecycline, daptomycin). The countries with the greatest number of such cases were RUS (n = 6 antibiotics), TUR (5), BLR (4), KAZ (4) and UKR (4).

Table 4. Antibiotics appearing in national lists that are not listed in the EML (non-EML antibiotics)

ALB	
Access	
Watch	cefaclor cefepime ● midecamycin oxytetracycline spiramycin teicoplanin
Reserve	tigecycline ●
Unclassified	nalidixic acid

ARM	
Access	
Watch	cefepime ● doripenem kanamycin ●
Reserve	
Unclassified	

AZE	
Access	ampicillin/sulbactam
Watch	lincomycin ofloxacin ●
Reserve	
Unclassified	furazidine furazolidone nitroxoline

BIH	
Access	
Watch	cefaclor cefepime ● kanamycin ● norfloxacin tobramycin
Reserve	tigecycline ●
Unclassified	

BLR	
Access	ampicillin/sulbactam oxacillin
Watch	cefaclor doripenem ertapenem erythromycin ● lincomycin midecamycin ofloxacin ●
Reserve	daptomycin ● tigecycline ●
Unclassified	benzathine benzylpenicillin/ benzylpenicillin combination (benzylpenicillin, benzathine benzylpenicillin, procaine benzylpenicillin)[a] combination (benzathine benzylpenicillin, procaine benzylpenicillin)[b] nitroxoline

KAZ	
Access	ampicillin/sulbactam cefadroxil tetracycline ●
Watch	cefamandole cefepime ● doripenem ertapenem erythromycin ● midecamycin ofloxacin ● rifaximin tobramycin
Reserve	
Unclassified	combination (benzylpenicillin, benzathine benzylpenicillin, procaine benzylpenicillin)[a] combination (benzathine benzylpenicillin, procaine benzylpenicillin)[b] fidaxomicin

KGZ	
Access	oxacillin
Watch	kanamycin ●
Reserve	
Unclassified	

MDA	
Access	tetracycline ●
Watch	cefaclor cefepime ● cefoperazone cefpodoxime proxetil lincomycin midecamycin norfloxacin ofloxacin ● roxithromycin
Reserve	
Unclassified	benzathine benzylpenicillin/ benzylpenicillin cefoperazone/ sulbactam ● furazidine

Table 4 contd.

	MKD	MNE	RUS	SRB
Access			ampicillin/sulbactam oxacillin	
Watch	cefaclor midecamycin orfloxacin pefloxacin	cefepime ● ertapenem fosnfomycin (oral) ofloxacin ●	cefepime ● ertapenem josamycin kanamycin ● lomefloxacin ofloxacin ● sparfloxacin tobramycin	cefaclor cefepime ● cefpodoxime proxetil cefprozil ertapenem fosfomycin (oral) midecamycin norfloxacin roxithromycin teicoplanin
Reserve		tigecycline ●	ceftaroline fosamil ● ceftolozane/ tazobactam daptomycin ● tedizolid telavancin tigecycline ●	tigecycline ●
Unclassified	benzathine phenoxymethylpenicillin nifuroxazide	benzylpenicillin/ procaine benzylpenicillin	cefoperazone/ sulbactam ●	benzylpenicillin/ procaine benzylpenicillin cefadroxil nifuroxazide pipemidic acid

	TJK	TUR	UKR	UZB
Access	ampicillin/ sulbactam trimethoprim ●	ampicillin/sulbactam sultamicillin tetracycline ●		tetracycline ●
Watch	cefepime ● kanamycin ● ofloxacin ●	cefaclor cefdinir cefepime ● cefoperazone cefpodoxime proxetil cefprozil ceftibuten dirithromycin ertapenem fosfomycin (oral) fusidic acid gemifloxacin lincomycin ofloxacin ● rifaximin roxithromycin spiramycin teicoplanin	cefepime ● fosfomycin (oral) kanamycin ● ofloxacin ●	cefepime ● cefoperazone josamycin ofloxacin ● pefloxacin roxithromycin spiramycin
Reserve		daptomycin ● tigecycline ●		
Unclassified		benzathine phenoxymethylpenicillin methenamine		cefoperazone/ sulbactam ● nifuroxazide nitroxoline

Removed from WHO EML ● Classified as Not recommended (AWaRe 2021) ●

[a] "Bicillin–3"

[b] "Bicillin–5"

Some 112 227 patients are treated on any given day with an antibiotic that has been removed from EML earlier editions for various reasons, such as, not considered essential, better options are available, increased resistance.

The most consumed antibiotics of this type were:

a. Access group: tetracycline (46 376 persons on any given day)
b. Watch group: ofloxacin (41 527), kanamycin (9089) and cefepime (5760)
c. Reserve group: tigecycline (867) and daptomycin (380)
d. Unclassified: ceftaroline-fosamil (72, only in RUS).

Discussion

This analysis found only partial concordance between national medicines selection lists and the EML. A likely explanation for this finding is that, firstly, NEMLs of seven countries (ARM, AZE, KGZ, GEO, RUS, UKR, UZB) and RLs of four countries (ALB, BIH, KGZ, TUR) included in this review had been published before 2020. Therefore, it is unlikely that the changes made in the 2019 EML were reflected in those lists. Similarly, there might have been a delay in withdrawing from national lists those antibiotics that had been removed from the EML. EML lists are dynamic, as new medicines arrive on the market and new evidence is published, leading to additions, changes, or removals. Following changes in the EML, there might have been delays between WHO recommendations and national implementation. Updates in the EML should be better disseminated, and the national lists need to be periodically revised, not only to add new medicines, but also to delete and rationalize.

Some medicines that appear in Table 4 were added to the EML in 2017 and then removed in the next iteration in 2019, as a consequence of a careful review of the 4th-generation cephalosporins (for example, cefepime) and 5th-generation cephalosporins (for example, ceftaroline-fosamil), tigecycline and daptomycin, as these antibiotics did not meet the revised criteria for inclusion in the Model Lists as individual Reserve group agents *(17)*. Kanamycin (which had originally been added to the EML in 1999) was also removed in 2019 during that review.

In 2013, the EML Expert Committee recommended replacing ofloxacin with levofloxacin in the antituberculosis medicines category, with a note to indicate that ofloxacin and moxifloxacin may be used as alternatives *(18)*. In 2017, the listing of fluoroquinolones was updated in line with the updated MDR-TB guidelines, and levofloxacin and moxifloxacin became the only fluoroquinolones suggested for MDR-TB in the EML. Finally, tetracycline was added in 1977 and removed in 1995, since doxycycline has a more favourable pharmacokinetic profile *(19)*.

Establishing mechanisms that ensure the updating of national medicines selection lists and the appropriate disseminating of changes and their rationale is critical to avoiding the prescribing of antibiotics that have become obsolete or that are no longer recommended. Deletions from the EML are as important as additions to the EML. Countries should take into account deletions from the EML when updating national medicines selection lists, clinical guidelines and formularies.

2. Antibiotics that have never been recommended in the EML

Of 1 343 637 persons treated with an antibiotic not included in the EML on any given day, 112 227 were treated with an antibiotic that was previously on the EML but has been removed. This leaves some 1 231 410 persons who receive an antibiotic that has never been in the EML. So, on any given

day, some 955 424 persons are treated with a Watch antibiotic that has never been recommended by WHO, and 256 000 persons are treated with an antibiotic that is not classified in the AWaRe system.

The antibiotics identified for this category can be classified into the following groups:

1. older penicillin combinations;
2. other combinations of antibiotics classified as 'Not recommended" by the EML Expert Committee;
3. antibiotics that belong to the same pharmacological class of those listed in the EML.

1) Older penicillin combinations

In numerous cases, where a country has not, strictly, listed the EML-recommended penicillin (such as, benzathine benzylpenicillin), then a combination that includes the recommended penicillin is listed; for example, MDA lists did not include benzathine benzylpenicillin but did include benzathine benzylpenicillin/benzylpenicillin combination. In this survey, BLR was the country with the greatest number of unclassified antibiotics in its national medicines selection list (n = 4 antibiotics).

Discussion

Combinations of penicillins (J01CE30) are commonly consumed in AMC Network countries; consumption levels ranged 0.01–0.07 DDD per 1000 inhabitants per day across 12 AMC Network countries *(13)*. It is possible that shortages of single-penicillin products have driven the usage of the combination products. Alternatively, usage could be related to the local clinical practice. It is worth investigating further the usage patterns for these products and updating national lists accordingly.

2) Other combinations of antibiotics classified as "Not recommended" by the EML Expert Committee

There were five countries (ALB, AZE, BIH, MNE, SRB) that did not consume any "Not recommended" fixed-dose combinations (FDCs), but the remaining 11 countries consumed one or more of these FDCs. Specifically, eight different FDCs were found and can be grouped as products containing a fluoroquinolone + an imidazole derivative, a 3rd-generation cephalosporin + a beta-lactamase inhibitor, or a combination of a macrolide + azole derivatives. Table 5 details the consumed amount per country of each of these groups.

Although the number of DDD per 1000 inhabitants per day are low or very low, some 44 228 individuals are being treated with one of these "Not recommended" FDCs each day in the studied countries. Among the countries included in this analysis, UZB (0.25 DDD per 1000 inhabitants per day), KGS (0.24) and GEO (0.23) were the top consumers of these products, although the highest volume of consumption in absolute terms was found in RUS (20 443 people treated on any given day), UZB (8594) and UKR (7888).

Table 5. Consumption of three groups of FDCs classified as "Not recommended" antibiotics

Agent	ARM	BLR	GEO	KAZ	KGZ	MDA	RUS	TJK	TUR	UKR	UZB
	Consumption in 2018 in DDD per 1000 inhabitants per day										
quinolone + imidazole derivatives	0	0.15	0.23	0.05	0.22	0.18	0.14	0.10	0.01	0.16	0.23
3rd-generation cephalosporin + beta-lactamase[a]	0	< 0.01	< 0.01	0	0	< 0.01	0	0	0	0.02	0
macrolide + fluconazole + secnidazole	< 0.01	0	0	0	0.02	0	< 0.01	0	0	0	0.02
Total	**< 0.01**	**0.16**	**0.23**	**0.05**	**0.24**	**0.19**	**0.14**	**0.10**	**0.01**	**0.18**	**0.25**
Agent	**ARM**	**BLR**	**GEO**	**KAZ**	**KGZ**	**MDA**	**RUS**	**TJK**	**TUR**	**UKR**	**UZB**
	Number of individuals treated with these products (population in 2018)										
Total (population in 2018)	**1 (2 963 230)**	**1511 (9 379 950)**	**866 (3 714 000)**	**845 (18 754 440)**	**1568 (6 591 600)**	**393 (2 072 530)**	**20 443 (144 104 080)**	**927 (9 537 640)**	**1192 (84 339 070)**	**7888 (44 134 690)**	**8594 (34 232 050)**

[a] Specific FDCs of a 3rd-generation cephalosporin and beta-lactamase inhibitor, which are neither evidence-based nor recommended in high-quality international guidelines, are included in the "Not recommended" list.

Discussion

These combination products have been categorized by the EML Expert Committee as "Not recommended", as have other FDCs of multiple broad-spectrum antibiotics, which are neither evidence-based nor recommended in high-quality international guidelines. Antibiotics in this group are FDCs that include a "Watch" antibiotic as one of their active ingredients. This means that, in addition to certain FDCs not being recommended because of poor evidence supporting their use, the FDCs include one antibiotic that should be preserved. Moreover, countries should investigate the usage patterns for these products because of their potential role in promoting multidrug-resistant bacterial infections *(15),* and endeavour to remove from clinical use those antibiotics that are in the "Not recommended" group. This could be done through, for example, updating national medicines selection lists, along with procurement lists, clinical guidelines and formularies.

3) Antibiotics that belong to the same pharmacological class of those listed in the EML

Most of the antibiotics included in Tables 4A and 4B belong in this broad category. It includes antibiotics not listed in any of the groups described earlier. As can be observed in Tables 4A and 4B, most of these antibiotics belong in the "Watch" group.

These antibiotics include me-too drug macrolides (such as, josamycin, midecamycin, roxithromycin and spiramycin), as well as quinolones for which there is less clinical experience (for example, pefloxacin, sparfloxacin, lomefloxacin). The countries listing the most antibiotics in this category were TUR (n = 14 antibiotics), SRB and KAZ (eight each), and MDA (seven).

Tables 6A, 6B, and 6C focus on the antibiotics of this type included in national lists. In the case of macrolides, for example, RUS, TUR and UZB listed three of these me-too drug macrolides in addition to azithromycin and clarithromycin. In the case of fluoroquinolones (Table 6B), RUS

listed three others in addition to ciprofloxacin (which is the only fluoroquinolone listed in the EML[3]); MDA, MKD, TUR and UZB listed two quinolones in addition to ciprofloxacin. There were 10 countries that listed ofloxacin; however, this may be related to its listing in an earlier EML, as an antituberculosis agent. Finally, in the case of the carbapenem derivatives (Table 6C), BLR and KAZ included ertapenem and doripenem, in addition to meropenem (or imipenem/cilastatin), the only carbapenem listed in EML. ARM, MNE, RUS, SRB, and TUR each listed one carbapenem in addition to meropenem.

Table 6A. Macrolides listed in the national medicines selection lists

Listing in EML	Macrolides listed in national medicines selection lists									
	ALB	BIH	BLR	KAZ	MDA	MKD	RUS	SRB	TUR	UZB
Macrolides listed in the EML	Azithromycin Clarithromycin									
Macrolides not listed in the EML	midecamycin spiramycin	tobramycin	midecamycin erythromycin	midecamycin tobramycin	midecamycin roxithromycin	midecamycin	josamycin tobramycin	midecamycin roxithromycin	dirithromycin roxithromycin	josamycin roxithromycin

Table 6B. Fluoroquinolones listed in the national medicines selection lists

Listing in EML	Fluoroquinolones listed in national medicines selection lists												
	AZE	BIH	BLR	KAZ	MDA	MKD	MNE	RUS	SRB	TJK	TUR	UKR	UZB
Fluoroquinolones listed in the EML	Ciprofloxacin												
Fluoroquinolones not listed in the EML	ofloxacin norfloxacin	norfloxacin	ofloxacin	ofloxacin	ofloxacin norfloxacin	norfloxacin pefloxacin	ofloxacin	lomefloxacin sparfloxacin ofloxacin	norfloxacin	ofloxacin	gemifloxacin ofloxacin	ofloxacin	ofloxacin pefloxacin

Table 6C. Carbapenems listed in the national medicines selection lists

Listing in EML	Carbapenems listed in national selection medicines lists						
	ARM	BLR	KAZ	MNE	RUS	SRB	TUR
Carbapenems listed in the EML	Meropenem[a]						
Carbapenems not listed in the EML	doripenem	doripenem ertapenem	doripenem ertapenem	ertapenem	ertapenem	ertapenem	ertapenem

[a] Imipenem/cilastatin is listed in BLR as an alternative to meropenem.

Discussion

Including numerous medicines with similar effects can create more space for marketing activity by the pharmaceutical industry, thus placing pressure on procurers, doctors and pharmacists. This can be even more problematic with Watch antibiotics, as there is a demonstrated relationship between their use and the appearance of multidrug-resistant bacteria. Moreover, having a greater number

3 Excepting the fluoroquinolones listed as antituberculosis medicines: levofloxacin and moxifloxacin.

of products in the national market implies an increased workload for the national drug regulatory agency, with regard to registration and quality assurance.

Fluoroquinolones are useful in the treatment of MDR-TB. Since 2017, levofloxacin and moxifloxacin have been the only fluoroquinolones listed in the EML for MDR-TB in line with the updated MDR-TB guidelines *(20)*. Countries should ensure that the national medicines selection lists are updated accordingly and that these quinolones are not used for common infections. Furthermore, as fluoroquinolones are Watch antibiotics and resistance to this group is increasing, it is important that countries listing them try to ensure their limited use according to updated national clinical guidelines. In fact, in 2019, the Committee for Medicinal Products for Human Use of the European Medicines Agency recommended restrictions on the use of fluoroquinolones in addition to suspension of the marketing authorization for medicines containing cinoxacin, flumequine, nalidixic acid and pipemidic acid *(21)*.

Is there a correlation between how many EML-recommended antibiotics are included in national medicines selection lists, and antibiotic consumption?

Proportion of antibiotic consumption according to inclusion in national medicines selection lists and by AWaRe classification

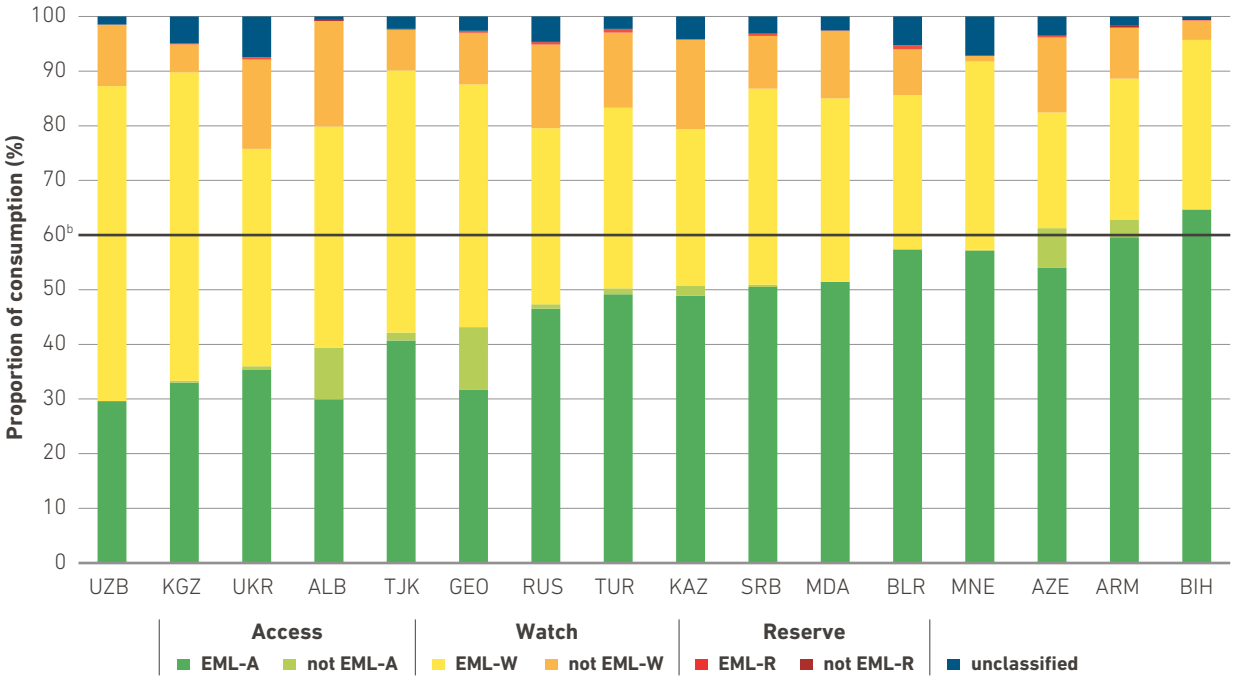
To analyse the correlation between antibiotic consumption and the listing of antibiotics in the national medicines selection lists, national antibiotic consumption patterns were examined. Fig. 1. breaks down antibiotic consumption by inclusion in national medicines selection lists and by AWaRe classification.

Estimates were made of the percentage of national antibiotic consumption broken down by AWaRe category and EML inclusion status:

- Access antibiotics in the EML
- Watch antibiotics in the EML
- Reserve antibiotics in the EML
- Access antibiotics not in the EML
- Watch antibiotics not in the EML
- Reserve antibiotics not in the EML.

In all the countries, the majority of antibiotic consumption consisted of antibiotics included in the EML, ranging from 70% (ALB) to 93% (BIH) of total antibiotic consumption. Consumption of antibiotics that are not included in the EML represented 4–30% of total antibiotic consumption; six countries (ALB, AZE, GEO, KAZ, RUS, UKR) showed 20–30%. In all countries except GEO, Watch group agents made up the majority of consumption of non-EML antibiotics. Most of the consumption of Watch antibiotics not included in the EML consists of cefaclor (2nd-generation cephalosporin), cefdinir (3rd-generation cephalosporin) and norfloxacin.

Fig. 1. Proportion of antibiotic consumption according to inclusion in the national medicines selection lists and by AWaRe classification in 2018[a]



[a] Antibiotic agents included for this calculation are those in antibacterials for systemic use (J01): neomycin (A07AA01), streptomycin (A07AA04), polymyxin B (A07AA05), kanamycin (A07AA08),vancomycin (A07AA09), colistin (A07AA10), rifamixin (A07AA11), rifampicin (J04AB02), rifamycin (J04AB03), rifabutin (J04AB04), metronidazole (P01AB01).

[b] The WHO indicator of at least 60% of total consumption being with Access antibiotics is displayed.

Discussion and limitations

Apart from three countries, the studied countries in 2018 did not achieve the WHO indicator of at least 60% of total consumption being with Access antibiotics. Generally, the majority of antibiotic consumption consisted of a small number of antibiotics. Reducing use of the most consumed Watch antibiotics, such as azithromycin and ciprofloxacin, is a key intervention for improving this indicator. Meanwhile, this analysis indicates that a significant proportion of antibiotic consumption, especially in the Watch group, is with antibiotics not included in the EML. The analysis highlights the importance of periodically updating which antibiotics are included in national lists, taking into account AMR patterns. It may be valuable to conduct further reviews on antibiotic inclusion in national medicines selection lists. The right choice of antibiotics in these lists requires considering the recommended antibiotics in the most recent national treatment guidelines for the most common infectious diseases. To realize improvements, up-to-date medicines selection lists need to be put into practice in the registration and procurement of antibiotics, and up-to-date treatment guidelines need to be disseminated to guide prescribers to the appropriate choice of antibiotics. Furthermore, disseminating the rationale for specific changes can help prescribers understand them and reduce prescription based on habits.

Owing to the differences in health system and consumption data sources among countries, it is difficult to make direct comparisons and rankings. Quantitative differences between countries should be considered only illustrative. However, DDD calculations are highly relevant for temporal analyses of individual countries.

CONCLUSION

Only medicines selection lists identified and chosen according to criteria were included in the analysis. Moreover, countries varied significantly in the types of medicines selection lists they used. International comparisons must, therefore, be treated with caution; identified apparently low concordance of national medicines selection lists with the EML may reflect the specific local role of such lists, rather than true unavailability of antibiotics in the national market.

Overall, the proportion of the EML-recommended antibiotics included in national medicines selection list(s) ranged between 26 and 85%. Most countries included over 50% of the EML-recommended antibiotics in their national medicines selection lists. Amoxicillin, amoxicillin with clavulanic acid (Access) and ciprofloxacin (Watch) were included in all 17 countries' lists. Certain EML-recommended antibiotics stood out in being included in national medicines selection lists significantly less often than others: cloxacillin (and its alternatives dicloxacillin and flucloxacillin), procaine benzylpenicillin and spectinomycin in the Access group, and oral vancomycin in the Watch group. In the Reserve group, most EML-recommended antibiotics were not listed in most countries. Although their usage should be limited according to WHO recommendations, essential Reserve antibiotics should be available in the national market for cases where other antibiotics have failed. Therefore, to ensure the appropriate use of Reserve antibiotics, it is critical that policies for their usage, infrastructure for policy implementation, and a monitoring system are in place prior to their introduction.

Inclusion levels varied notably between AWaRe groups. For Access group antibiotics, the median inclusion rate was 80% (range 25–100%). Similarly, for Watch group antibiotics, the median rate was 83% (range 25–100%). Inclusion levels were lower for Reserve group antibiotics, with a median inclusion rate of 14% (range 0–29%).

Other than the Ukraine list, none of the national medicines selection lists reviewed in this analysis used the AWaRe system or employed "primary/secondary"-type categorization to formulate a different prioritization system for antibiotics (for example, first-line versus second-line). The AWaRe classification is recommended as a tool for antibiotic stewardship, with its value reinforced by a recent systematic review showing that the emergence of AMR is much more closely linked to the use of Watch and Reserve group antibiotics, than to the use of Access group antibiotics *(15)*.

The relevance of non-listed EML antibiotics differs according to the availability of other recommended alternatives and the consequences depend on the specific antibiotic and its recommended use. Absence of Access antibiotics such as phenoxymethylpenicillin and nitrofurantoin with a low resistance potential can lead to misuse of less preferred alternatives such as macrolides or fluoroquinolones (Watch antibiotics). Switching to Watch group antibiotics is associated with an increase in bacterial resistance. However, the picture is complicated by possible global shortages of penicillins.

Some national medicines selection lists included antibiotics that had been removed from the EML earlier editions. It is important that WHO ensures that countries are aware of changes in the EML, and national medicines selection lists need to be periodically revised not only to add but also to remove medicines that are no longer the standard of care. Fluoroquinolones are useful in the treatment of MDR-TB. Since 2017, levofloxacin and moxifloxacin have been the only fluoroquinolones listed in the EML for MDR-TB in line with the updated MDR-TB guidelines. However, ofloxacin, which was previously recommended for MDR-TB, is listed in national lists of 10 countries. Countries should ensure that the

national medicines selection lists are updated accordingly, and that the two quinolones for MDR-TB are not used for common infections. Establishing mechanisms that ensure the updating of the NEML (and other relevant lists) and appropriately disseminating the rationale for changes are critical in reducing the prescribing of antibiotics that have become obsolete or are no longer recommended. Countries should take into account deletions from the EML when updating national medicines selection lists, clinical guidelines and formularies.

Certain antibiotics, which are not included in the EML or in the AWaRe system, such as combinations of penicillins (J01CE30), are commonly consumed in AMC Network countries. It may be possible that shortages of single-penicillin products have contributed to the usage of the combination products. Use of combination penicillins may also be related to local clinical conventions. Similarly, some national medicines selection lists include antibiotics that are considered "Not recommended" in the EML. These are FDCs of multiple broad-spectrum antibiotics, whose use is neither evidence-based nor recommended in high-quality international guidelines (for example, the combination of quinolones with imidazole derivatives–J01RA). Countries should endeavour to remove from clinical use those antibiotics that are in the "Not recommended" group.

Many of the non-EML antibiotics included in national medicines selection lists belong in the "Watch" group. The consumption of antibiotics not listed in the EML makes up as much as 20–30% of total antibiotic consumption in some countries, and most of this consumption represents Watch antibiotics. Recent studies have underscored the relationship between the consumption of Watch antibiotics and the development of multidrug-resistant bacteria. Countries should take into account these findings as they revise and update their national lists. While reducing use of the most consumed Watch antibiotics is a key intervention for improving the national monitoring target, the analysis highlights the importance of updating the antibiotics included in the national medicines selection lists, taking into account the AMR patterns. It may be valuable to conduct further reviews on antibiotic inclusion in national medicines selection lists. The right selection of antibiotics in national medicines selection lists also requires considering the recommended antibiotics in the most recent national treatment guidelines for the most common infectious diseases. To realize improvements, up-to-date medicines selection lists need to be put into practice in the registration and procurement of antibiotics, and up-to-date treatment guidelines need to be disseminated to guide prescribers to choose appropriate antibiotics. Furthermore, disseminating the rationale for specific changes can help prescribers understand them and reduce prescribing based on habits.

Patterns of antibiotic use can be affected by an overly narrow range of available antibiotics, as well as an overly broad range of available antibiotics. On the one hand, the unavailability of recommended first-choice antibiotics (such as, nitrofurantoin) can lead to the systematic prescription of second-choice options for the same indication; unfortunately, many of these alternatives belong in the Watch category (for example, fluoroquinolones). On the other hand, an over-representation of some therapeutic groups such as macrolides, fluoroquinolones or 3rd- and 4th-generation cephalosporins could be related to a higher consumption of these groups. To try to mediate between both extremes, the national medicines selection lists together with clinical practice guidelines can serve to create and maintain an environment that promotes appropriate use of antibiotics.

Including numerous medicines with similar effects can create more space for marketing activity by the pharmaceutical industry, thus placing pressure on procurers, doctors and pharmacists. Moreover, having a greater number of products in the national market implies an increased workload for the national drug regulatory agency, with regards to registration and quality assurance.

It is recommended that countries regularly review national medicines selection lists and further examine the potential issues identified in this review, taking into account the roles of the lists and the local contexts.

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ISBN 978-92-890-5858-2